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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,621	01/05/2000	Stephen E. Epstein	674522-2001	1917

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/478,621	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment and response filed on 27 February 2004 is acknowledged and entered. Following the amendment, claims 1, 3-5, 8-17, and 26-33 are canceled, and claims 18, and 20-24 are amended.

Currently claims 18-25 are pending, and under consideration.

The declaration under 37 CFR 1.132 filed on 27 February 2004 is sufficient to overcome the rejection of claim 22 based upon the specific references applied under 35 U.S.C. 103 for the following reasons:

In items 3-6, it is stated that atherosclerosis and restenosis are not the same condition; that although they share several pathophysiological components leading to luminal narrowing of an artery, it does not mean that inhibiting the development of any of these components will have the same effect on restenosis as on atherosclerosis; that atherosclerosis is a *chronic* process, whereas restenosis is an *acute* process, and the vessel wall responses to both would be very different; that the prior art by Pels 1 indicates that adventitial microvessels can have beneficial impact on the maintenance of arterial lumen after an acute injury, which is just the opposite of what is taught in the current application, and *teaches away* from the claimed invention. This argument is persuasive, and the prior art rejection of claim 22 is overcome.

Said declaration is ineffective to overcome the rejection of claims 18-21 and 23-25 based upon the specific references applied under 35 U.S.C. 103 as set forth in the last Office action for the reasons below under "***Rejections Over Prior Art***".

Withdrawal of Objections and Rejections:

All objections and rejections of claims 1, 3-5, 8-17, and 26-33 are moot as the applicant has canceled the claims.

The rejection of claims 18-25 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

The prior art rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Inoue et al. (Circulation, Nov. 1998, 98(20): 2108-16), and Maisonpierre et al. (Science, July 1997, 277:55-60), in view of Kendall et al. (US 5,712,380), Asahara et al. (Circ. Res., 1998, 83: 233-240), and Hanahan (Science, 1997, 277: 48-50) is withdrawn in view of applicant's declaration, amendment, and argument.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 22 is directed to a method for reducing restenosis of coronary or peripheral vessels using a VEGF inhibitor and a protein agent for inducing vessel maturation. However, the specification discloses the in vitro study of pig coronary vessels injured by balloon angioplasty, wherein the vessels are obtained at different time points after the injury or at different time points after the treatment with adenoviral vectors expressing soluble VEGF-R, and ang-1 following the injury, and merely mentions that multiple known angiogenesis factors and neointimal mass are measured (Example 2). The specification does not provide any experimental result showing restenosis and reduction thereof. Figure 2 in the specification is noted, however, it does not appear to represent actual data, but rather appears to be a prophetic drawing, and it does not show any indication of restenosis. Thus, it is not even clear whether restenosis ever happened in these animals, or if it did, what is the incident rate, as it is known, and indicated in the present

specification on page 4, that restenosis does not happen in all patients who had angioplasty, and the reasons remain unclear. Therefore, there would not be predictable as to which animal would develop restenosis following the injury, and thus, it is critical to show the rate of occurrence of restenosis, and the reduction of such restenosis when the *claimed method* is applied.

Further, the specification provides no working example as to using *a protein* agent for inhibiting VEGF and *a protein* agent for inducing vessel maturation as claimed. The working example 2 is a method of gene therapy, wherein adenoviral vectors expressing soluble VEGF-R, and ang-1 following the injury were applied for the treatment. Gene therapy is different from protein therapy as it requires the production of the encoded protein in vivo first in order to achieve any desired effect. In the instant case, it is unclear whether the transgenes of the adenoviral vector administered were ever expressed. Therefore, it is impossible for one of skilled in the art to determine from the example 2 whether the gene therapy worked at all, how well it worked if it were effective, and whether the *claimed* method of *protein* therapy would work at all. Contrary to the claimed method, the prior art references by Pels et al. (Japanese Circulation Journal, 1997, 61 (11): 893-904; Arterioscler. Thromb. Vasc. Biol., 1999, 19:229-238), cited in applicants declaration, indicates that advantitial microvessels can have a beneficial impact on the maintenance of arterial luman after an acute vessel injury. Therefore, the prior art teaches against inhibiting such vessel formation, as would result from the claimed method. As such, it is highly unpredictable whether the present method would be beneficial for treating restenosis, and undue experimentation would be required prior to practice the claimed invention.

Due to the large quantity of experimentation necessary to determine whether the protein agents of the claims would be effective for the treatment of restenosis; the lack of working examples directed to same, the absence of evidence to support the occurrence of restenosis, the expression of the transgene, and the reduction of the restenosis following the gene therapy; the complex nature of the invention; the state of the prior art indicating that advantitial microvessels have a beneficial impact on the maintenance of arterial luman after the injury; the lack of predictability; undue experimentation would be required of the skilled artisan to use the claimed invention.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21 and 23-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Inoue et al. (Circulation, Nov. 1998, 98(20): 2108-16), and Maisonpierre et al. (Science, July 1997, 277:55-60), in view of Kendall et al. (US 5,712,380), and Asahara et al. (Circ. Res., 1998, 83: 233-240), for the reasons set forth in the previous Office Actions, paper No. 9, 13, and 20.

Applicants declaration and argument filed on 27 February 2004 have been fully considered, but is not deemed persuasive for reasons below.

The present claims 18-21 and 23-25 are directed to a composition and a kit thereof for reducing restenosis of coronary or peripheral vessels. Applicants argue, at pages 2-4 of the response, that restenosis and atherosclerosis are distinct conditions, and have independent mechanisms, and that the cited prior art references are related to atherosclerosis, and make no connection between athrosclerosis and restenosis. In addition, Applicants declaration also indicates that the prior art by Pels 1 teaches away from the claimed invention. This argument is not persuasive because for the reasons of the record set forth in the previous Office Actions, it would be obvious to make a composition combining a VEGF inhibitor such as soluble VEGF-R, and Ang1 at least for the purpose of treating athrosclerosis (as the canceled claims 1-5, for

example). Although applicants have canceled the claims directed to the same composition (for the treatment of athrosclerosis), and the remaining claims 18-21 and 23-25 recite a different use of the composition, i.e., for reducing restenosis (other than athrosclerosis), it is merely of an intended use, which does not alter the nature of the composition. Therefore, such claim limitation adds no patentable weight to said composition.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
5/10/04